REMARKS

Claims 1-15 and 17-20 are pending in this application. Claims 1-12 and 18-20 stand rejected and claims 13-15 and 17 were withdrawn from consideration. Reconsideration and allowance of the claims is respectfully requested in view of the following remarks.

Applicants also wish to draw to the Examiner's attention co-pending application US Application No. 11/579,675 which application is titled "Antisolvent Emulsion Solidification Process."

INFORMATION DISCLOSURE STATEMENT

The Examiner has requested an English translation of DE3818453. Attached hereto is the Derwent Abstract (in English) for DE3818453 and a mechanical translation of DE3818453.

REJECTIONS UNDER 35 U.S.C. § 103(a)

Claims 1-3, 5-8, 10, 18 and 20 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jakupovic et al. (US Patent 6,221,398) in view of Subramaniam et al (US Patent No.: 6,113,795). Applicants traverse this rejection for the reasons provided herein below.

This instantly claimed process provides a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a membrane into one or more antisolvents, or vice versa. The membrane is used as a precision dosing device through wich liquid medium comprisining one or more organic compounds is forced into antisolvent or visa versa. Use of the membrane as a precision doing device allows for efficient micromixing of the liquid medium comprising at least one dissolved compound and one or more antisolvents and continuous operation (see, e.g., paragraph [47] of the published US patent application, Publication No.: US2006/018280800).

Jakupovic et al relates to a batch process for producing a pharmaceutical powder for inhalation. In Jakupovic et al an inhalation compound is dissolved in a solvent which is introduced in droplet form or as a jet stream into an antisolvent under agitation and non-

supercritical conditions (see column 2, lines 26 to 34 of Jakupovic et al). The solution is introduced into the antisolvent through a porous filter or one or more nozzles.. Exemplified are batch-type preparation processes which use Pyrex Glass Filters having a pore index from 10 microns to 160 microns (see Examples 1-8, columns 5 and 6). Jakupovic et al does not teach or suggest the use of a membrane as a precision dosing device in a continuous system.

Subramaniam et al uses a feed section (12), a precipitation unit (14) which includes a recrystallization chamber (32) and a particle separation section (16). In operation the drug and solvent are introduced by a pump (18) via a nozzle (40) into the precipitation chamber (32) while supercritical carbon dioxide is flowed through an annulus of the nozzle into the precipitation chamber (32) dispersing the drug solution into tiny droplets thereby causing the drug to precipitate (column 6, lines 1-15). Thus, Subramaniam et al does not teach or suggest the use of a membrane as a precision dosing device in a continuous system. Instead, Subramanian et al utilizes a membrane further downstream in the system as a means of separating particles from the solvent and antisolvent.

The Examiner alleges that "[t]he skilled artisan would have been motivated to use a membrane having up to 3 um pore size and the shape of the membrane is selected from tubes, fibres, and spiral wounds in such a process because Subramaniam et al teach that those skilled in the art appreciate that the average pore size can be adjusted to suit a particular application." (see Office Action , bridging paragraph on pages 5 and 6). Applicant respectfully disagrees.

The skilled artisan would not have been motivated to substitute the Jakupovic et al flat glass filter for a membrane because the skilled artisan would not reasonably expect that a flat membrane would be able to withstand the pressure drop over the membrane when used as a dosing device through which liquid medium or antisolvent is forced. In Subramanian et al the flat membrane filter is used as a separation device and therefore not subject to the same pressure drop. Thus, there was no reasonable expectation of success that the flat membrane would work as a dosing device. Accordingly, the skilled artisan would not have been motivated to use a flat membrane in a continuous method as a precision dosing device. The use of membranes in a continuous system having up to 3 μm pores and shapes selected from tubes, fibres, and spiral wounds, to achieve uniform particle size and avoiding uncontrolled precipitation of solids and the formation of agglomerated particles is found only in the instant application. Accordingly, withdrawal of this rejection is respectfully requested.

Also, as presented previously by Applicant, the instantly claimed process using a pore size of up to 3 μm pores surprisingly can produce particles having a d50 larger than the pore size. For example, use of a 1 μm pore filter, resulted in an average crystal size of d50 of 40 μm (see Example 1, paragraphs [79] -[82]) and a d50 ranging from 7 to 42 μm depending on the flow rate (see Example 2, paragraphs [83] to [89]). In addition, the instantly claimed process can be easily scaled up for commercial production while maintaining robust control of the particle size (see, e.g., paragraph [15]) by allowing for the ratio of solvent to antisolvent to be controlled thereby resulting in more uniform particle size (see, e.g paragraphs [15] and [55]) and avoiding uncontrolled precipitation of solids and the formation of agglomerated particles (see, e.g., paragraphs [15], [20]). Accordingly, withdrawal of this rejection is respectfully requested.

The Examiner cites *In re Dilnot*, 319F.2d188, 138USPQ248 (CCPA1963) as holding that claims directed to a continuous process would have been obvious in light of a batch process of the prior art. (See Office Action, page 4) and therefore that it would have been *prima facie* obvious to go from the batch process of Jakupovic et al to a continious process. Applicant respectfully disagrees for the reasons presented herein below.

Several claims were under appeal in *In re Dilnot,* including claim 22 which related to the production of cementitious material by continuous introduction of foam. The court determined that claim 22 was obvious because continuous operation was the only feature relied on by the Appellant used to distinguish the production of cementitious material from the art cited in the case. First, Applicant respectfully submit that continuous production of cementitious material is not analogous to the continuous production of particles for use in pharmaceuticals. Thus, the facts in *In re Dilnot* are not analogous to the facts in the instant application, such as, for example in the use of membrane filters as a dosing device . In addition, as set forth herein above, Applicant has provided other indicia of non-obviousness. Specifically, that there was no reasonable expectation of success that the glass filter of Jakupovic could be substituted with a flat membrane because the skilled artisan would not reasonably expect that a flat membrane would be able to withstand the pressure drop over the membrane when used as a dosing device through which liquid medium or antisolvent is forced. Further, the instantly claimed process using a pore size of up to 3 μm pores surprisingly and unexpectedly can produce particles having a d50 larger than the pore size. Accordingly, Applicant respectfully submits that the Examiner has not met his evidentiary burden for a *prima facie* case. Withdrawal of this rejection is respectfully requested.

Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jakupovic et al in view of Subramaniam et al and further in view of Nocent et al.(*J. Pharm. Sci*, 90, 1620-1627). Applicants traverse this rejection for the reasons provided herein below.

For the reasons stated herein above and of record, Jakupovic et al and Subramaniam et al, either alone or in combination, do not render the claimed process obvious. Nocent et al relates to the type of solvent, antisolvent and emulsifier and the concentration of the emulsifier for the production of spherical crystals of salbutamol sulfate (see, abstract). Nocent et al does not does not teach or suggest a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a membrane in a membrane module into one or more antisolvents, or vice versa. Accordingly, Nocent et al does not remedy the deficiencies of either Jakupovic et al and/or Subramaniam et al. Withdrawal of this ground of rejection is respectfully requested.

Claims 1, 8 and 9 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jukapovic et al in view of Sabramaniam et al and in view of Chen et al (US Patent 7,374,779) as evidenced by Nakagawa et al. (*Japan J. Pharmacol.* 29, 509-514, 1979). Specifically the Examiner alleges that Chen et al cures the deficiency of Jakupovic et al and Subramaniam et al by teaching a process for forming progesterone or 3-ketodesogestrel crystal particles. Applicants traverse this rejection for the reasons provided herein below.

Chen et al relates to pharmaceutical formulations and systems for improved absorption and multistage release of active agents. Chen et al generally discusses a variety of techniques for manufacturing the active agent, including crystallization by dissolution in appropriate solvents (see column 54, lines 35-37). The focus of Chen et al is formulations and systems for improved absorption of agents. Chen et al does not teach or suggest a continuous antisolvent solidification process which uses a membrane as a precision dosing device to introduce at least one dissolved organic or inorganic compound in a solvent into one or more antisolvents, or vice versa. Such a teaching is found only in the instant application. Thus, Chen et al fails to cure the deficiencies of either of Jakupovic et al and/or Subramaniam et al. Accordingly, either alone or in combination, Chen et al does not render the claimed invention obvious.

Nakagawa et al relates to anti-inflammatory action of progesterone in a rat model. Nakagawa et al does not teach or suggest a a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a membrane in a membrane module into one or more antisolvents, or vice versa. Accordingly, Nakagawa et al either alone or in combination does not render the claimed invention obvious.

Claims 1, 11 and 12 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jukapovic in view of in view of Sabramaniam et al and Maruyama et al (US Patent 5,512,092,). Specifically, the Examiner alleges that it would have been *prima facie* obvious to modify the teachings of Jakupovic et al and Subramaniam et al. by coating the solid particles, because Maruyama teaches coating pharmaceutical solids utilizing drug coating materials. Applicants traverse this rejection for the reasons provided herein below.

Maruyama et al relates to a method for preparing an aqueous emulsions for coating solid pharmaceutical preparations. In Maruyama an emulsified stock solution is concentrated by removing a part of the liquid components while passing it through a membrane for ultrafiltration (see Maruyama et al abstract). Maruyama et al does not teach or suggest a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a precision dosing membrane into one or more antisolvents, or vice versa. Thus the teachings in Maruyama fail to cure the deficiency in the teachings of Jakupovic and/or Sabramaniam et al as described above.

Claims 1, 18 and 19 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Jukapovic in view of in view of Sabramaniam et al and Siam et al (US Patent 6,851,166). Specifically, the Examiner contends that it would have been *prima facie* obvious to modify the teachings of Jakupovic et al and Subramaniam et al. by preparing the dosage in the form of tablets because Saim et al teaches that such particles can be prepared in the form of tablets. Applicants traverse this rejection for the reasons provided herein below.

Saim et al relates to a method of small particle precipitation wherein the solute partyicles are precipitated from a pressurized gaseous fluid or solution or a liquid solution and retained and dispersed in a carrier. Saim et al does not teach or suggest a continuous antisolvent solidification process where a liquid medium comprising at least one dissolved organic or inorganic compound is introduced through a membrane into one or more

antisolvents, or vice versa. As Saim et al does not remedy the deficiencies of the cited references, Saim et al does not render the claimed invention obvious. Withdrawal of this rejection is respectfully requested.

CONCLUSION

It is believed that claims are now in condition for allowance, early notice of which would be appreciated. If any outstanding issues remain, the examiner is invited to telephone the undersigned at the telephone number indicated below to discuss the same. In the event the United States Patent and Trademark Office determines that an additional extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with this filing to Deposit Account No.: 50-4205 ; Reference Number: 2003.817USD1.

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